PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
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ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 June 2000 (15.06.00)	
International application No. PCT/EP99/07928	**Applicant's or agent's file reference** O/98411 WO
International filing date (day/month/year) 19 October 1999 (19.10.99)	**Priority date** (day/month/year) 23 October 1998 (23.10.98)
Applicant TIMMERS, Cornelis, Marius et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:
   17 May 2000 (17.05.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Villet
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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Form PCT/IB/331 (July 1992)

NOBEL

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
O/98411 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/07928	19/10/1999	23/10/1998
International Patent Classification (IPC) or national classification and IPC C07D217/22		
Applicant AKZO NOBEL N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17/05/2000	19.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fanni, S Telephone No. +49 89 2399 8712

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07928

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-31 as originally filed

Claims, No.:

1-8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-8
	No:	Claims
Inventive step (IS)	Yes:	Claims 3-5
	No:	Claims 1, 2, 6-8
Industrial applicability (IA)	Yes:	Claims 1-8
	No:	Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

ITEM V

Reference is made to the following documents:

D1: EP-A-0 064 294
D2: WO 97 38977 A
D3: EP-A-0 393 926
D4: WO 98 47876 A

NOVELTY (Article 33(2) PCT)

The present subject matter differs from D1 mainly on account of the present residues E and D as described in present claim 1 and on account of the oxo-substituent which is on position 6 of the present benzo-fused moiety, said substituent being in position 5 on the isoquinoline derivatives disclosed by D1.

The present subject matter differs from D2 mainly on account of the present residues E-D-J on the 6-oxo substituent (see definition of R1 in claim 1 of D2).

The present subject matter differs from D3 mainly on account of the present residues E-D-J, (see definition of R1 in claim 1 of D3), and on account of the unsubstituted amino group ever present in compounds of formula I according to present claim 1.

Provided that the claimed priority is valid, D4 is not a relevant document for PCT examination (see item VI below). The opinion given herein could however be relevant during the national phase:

The present subject matter is considered as a selection of the subject matter disclosed by D4. The derivatives disclosed by D4 have a medical application, namely as antithrombotic agents.

INVENTIVE STEP (Article 33(3) PCT)

D1 is considered the structurally closest prior art and discloses 1, 5-substituted

isoquinolines derivatives suitable for treating hypertension, from which the present subject matter differs, as said above, on account of the residues E and D as described in formula I according to present claim 1 and of the oxo-substituent which is on position 6 of the present benzo-fused moiety.

The problem to be solved by the present application is considered to be the provision of thrombin inhibitor of formula (I) according to present claim 1.

The problem has been solved, at least in vitro, as shown by the example 15 reported on pages 29-31 of present description.

None of the above said prior art documents provides information which would lead the skilled person to consider compounds of formula (I) according to present claim 1 as a solution for the aforementioned given problem. Thus, the present subject matter could be considered based on an inventive step.

It is however pointed out that it must be made credible that essentially all of the claimed matter solves the given problem and that only the compounds which are suitable for solving the problem underlying the present subject matter could be claimed . This is not the case with present claims 1-2, since the scope of residues E and J in said claims is much broader than those revealed by the specific examples reported in the present description (see example 1-14, pages 12-29 of present description). In view of this fact, the technical problem which is considered to be solved by part of the compounds falling within the scope of claim 1 is merely the provision of further chemical compounds, the solution of which could not be considered inventive. For this reason, an inventive step cannot be acknowledged for present claim 1, and its dependent claims 2 and 6-8.

Therefore, an inventive step can be acknowledged only for the present claims 3-5.

ITEM VIII

The expression "serine protease inhibitor" as used in present claims could be interpreted as being a limiting feature of the claimed compounds, (i. e. only the compounds which acutally are serine proteases are claimed) which defines the subject matter in terms of desired properties and therefore introdueces unclarity in the claims

(Article 6 PCT).

The term "prodrug" as used in claim 1 is a functional expression, i.e. an expression attempting to define the subject matter in terms of a desired property; said claim does not fulfil therefore the requirements of Article 6 PCT.

The meaning of labels Tic, Atc, Aic and Piq, used in claim 1, is not explained in said claim.

In example 1, the nomenclature of camphor derivatives is ambiguous since it is not clear wether the camphor residue is a 8 sulphonyl or a 10 sulphonyl derivative.

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant *(for all designated States except US)*: AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL-6824 AB Arnhem (NL).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TIMMERS, Cornelis, Marius [NL/NL]; De Bongerd 132, NL-5345 JW Oss (NL). REWINKEL, Johannes, Bernardus, Maria [NL/NL]; Bram van de Berghstraat 23, NL-5348 JT Oss (NL).

(74) Agent: HOGENBIRK, M.; P.O. Box 20, NL-5340 BH Oss (NL).

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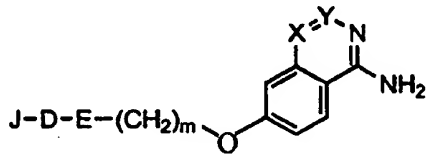
Published
With international search report.

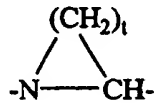
(54) Title: SERINE PROTEASE INHIBITOR

(57) Abstract

The invention relates to a serine protease inhibitor having formula (I), in which J is H, R^1, R^1-O-C(O)-, R^1-C(O)-, R^1-SO_2-, R^3OOC-$(CHR^2)_p$-, (R^{2a}, R^{2b})N-CO-$(CHR^2)_p$- or Het-CO-$(CHR^2)_p$-; D is an amino-acid of the formula -NH-CHR^1-C(O)-, -NR^4-CH[$(CH_2)_q$C(O)OR^1]-C(O)-, -NR^4-CH[$(CH_2)_q$C(O)N(R^{2a},R^{2b})]-C(O)-, -NR^4-CH[$(CH_2)_q$C(O)Het]-C(O)-, D-1-Tiq, D-3-Tiq, D-Atc, Aic, D-1-Piq or D 3-Piq; E is -NR^2-CH_2 or the fragment (a), optionally substituted with (1-6C)alkyl, (1-6C)alkoxy or benzyloxy; R^1 is selected from (1-12C)alkyl, (2-12C)alkenyl, (2-12C)alkynyl, (3-12C)cycloalkyl and (3-12C)cycloalkyl(1-6C)alkylene, which groups may optionally be substituted with (3-12C)cycloalkyl, (1-6C)alkoxy, oxo, OH, CF_3 or halogen, and from (6-14C)aryl, (7-15C)aralkyl, (8-16C)aralkenyl and (14-20C)(bisaryl)alkyl, whereby the aryl groups may optionally be substituted with (1-6C)alkyl, (3-12C)cycloalkyl, (1-6C)alkoxy, OH, CF_3 or halogen; R^2, R^{2a} and R^{2b} are each independently selected from H, (1-8C)alkyl, (3-8C)alkenyl, (3-8C)alkynyl, (3-8C)cycloalkyl and (3-6C)cycloalkyl(1-4C)alkylene, which can each be optionally substituted with (3-6C)cycloalkyl, (1-6C)alkoxy, CF_3 or halogen, and from (6-14C)aryl and (7-15C)aralkyl whereby the aryl groups may optionally be substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF_3 or halogen; R^3 is defined for R^2 or Het-(1-6C)alkyl; R^4 is H or (1-3C)alkyl; X and Y are CH or N with the proviso that they are not both N; Het is a 4-, 5- or 6-membered heterocycle containing one or more heteroatoms selected from O, N and S; m is 1 or 2; p is 1, 2 or 3; q is 1, 2 or 3; t is 2, 3 or 4; or a prodrug; or a pharmaceutically acceptable addition salt and/or solvate thereof and its use in therapy and manufacture of a medicament for treating or preventing thrombin-mediated and thrombin-associated diseases.



(I)



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